جامعة الملك سعود
King Saud University

Biochemistry437

Globular proteins

Biochemistry Team 437

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Objectives:

- To describe the globular proteins using common examples like hemoglobin and myoglobin.
- To study the structure and functions of globular proteins like:
  - Hemoglobin (a major globular protein).
  - γ-globulins (immunoglobulins)
  - Myoglobin
- To know the different types of hemoglobin and difference between normal and abnormal hemoglobin
- To understand the diseases associated with globular proteins .

- Proteins are polymers of amino acids that are joined by peptides bond, then folded in a proper way to make a functional unit.
- The sequence of amino acids determines the final structure (shape) of a protein.
- The Structure can either be: 1-globular (spherical) or 2-fiber (rope like structure).
- The structure determines the function.
- Rope like = structural functions like support and transport, they are not water soluble e.g. collagen
- Globular (spherical) = water soluble, so they can participate in systemic reactions and interact with metabolites. E.g. Enzymes

Globular proteins:

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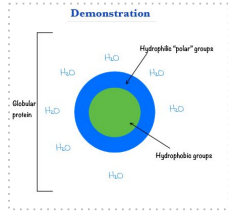
Amino acid chains fold into shapes that resemble spheres are called globular proteins

This type of folding increases solubility of proteins in water.(because)



1- Polar"hydrophilic" groups on the protein's surface

increases the solubility

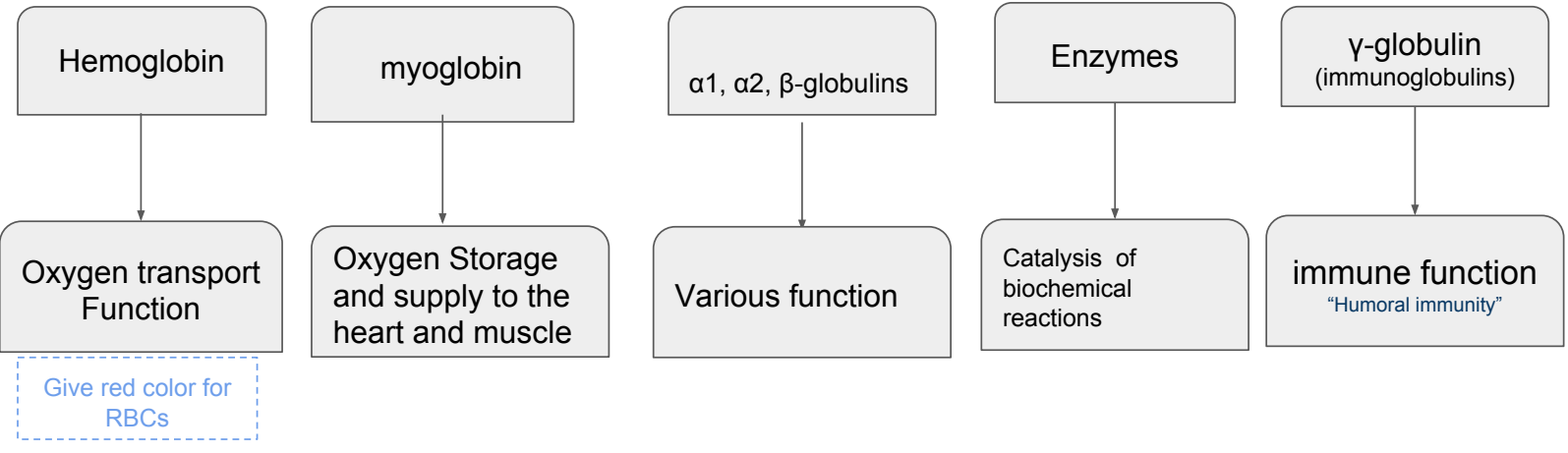
2- Hydrophobic (non- polar) groups in the interior (داخل البروتين)

increases stability of the structure

Fibrous proteins(collagen) are mainly insoluble structural proteins

Globular proteins

There are mainly 3 types of globular proteins , (α Alpha, β Beta , γ Gamma). These subunits have their own subtypes and combine together to make other types of globular proteins. E.g. hemoglobin is made of 2 α and 2β subunits.



Hemoglobin

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A major globular protein in humans

Composed of four polypeptide chains.

- Two α and two β chains
- Contains two dimers of αβ subunits

Held together by non-covalent interactions

Each chain is a subunit with a heme group in the center that carries oxygen

A Hb molecule contain 4-heme groups and carries 4 molecules of O2

Or 8 atoms of O2

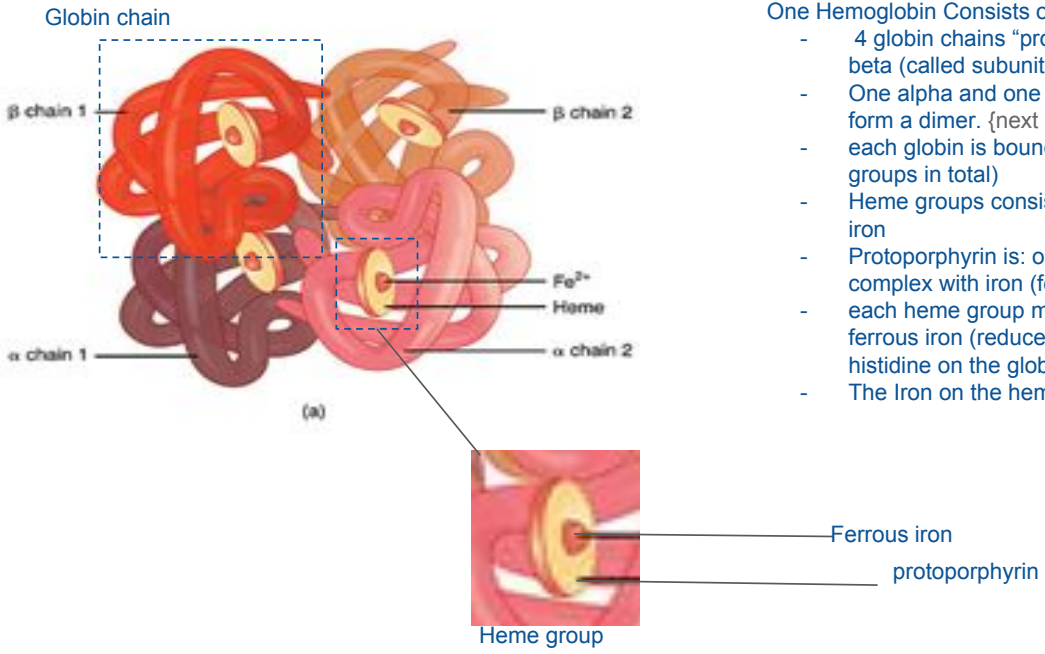
Extra :Haemoglobin formation does not occur randomly. but first the alpha chain binds with the Beta chain forming a dimer. Two dimers form haemoglobin (a&b dimer)2

Types of hemoglobin

Normal (Can carry O2)	Abnormal (Can not carry O2)
HbA: (97%) (Adult)	Carboxy Hb
HbA2: (2%)	Met Hb
HbF: (1%) (fetal) (Fetal HB)	Sulf Hb
HbA1c	

More details are discussed later in the lecture

Structure of hemoglobin



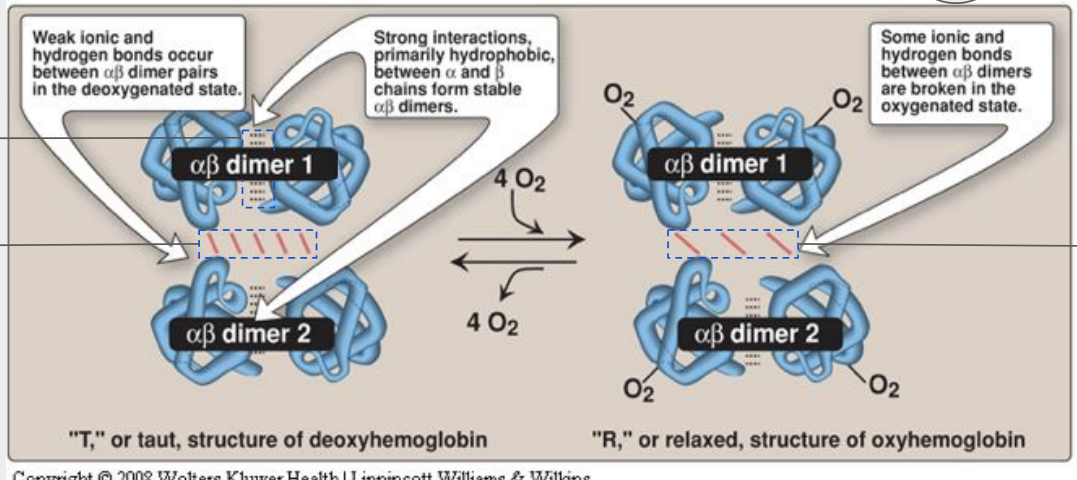
One Hemoglobin Consists of:

- 4 globin chains “protein chains” two alpha and two beta (called subunits)
- One alpha and one beta subunti bind together to form a dimer. {next slide}
- each globin is bound to one heme group. (4 heme groups in total)
- Heme groups consists of protoporphyrin + ferrous iron
- Protoporphyrin is: organic compound forming a complex with iron (fe2)
- each heme group makes two bonds, 1- with a ferrous iron (reduced form of iron “F+2”) 2-with the histidine on the globin
- The Iron on the heme group binds to O2

HbA structure

2 dimers each dimer consists of 2 subunits

There are two types of HbA:



Hydrophobic bonds

Weaker ionic bonds between dimers (interdimer)

Notice that there is a lesser number of ionic bonds because the rest were broken after O2 was bound to it

1-deoxyhemoglobin,T(taut) :

-deoxygenated state (no O2 bound to it)

-Strong intradimer hydrophobic bonds Between the subunits

-weaker ionic bonds between dimers, these bonds make it **T(taut) (tight)** (مشدود) and causes less movement

2-Oxyhemoglobin,R(relaxed):

-oxygenated state .

- when O2 binds to it, some of the ionic bonds are broken, so the structure becomes more relaxed and allows for more movement.

Note for previous slide :The first oxygen molecule that binds with haemoglobin will be the hardest because of the conformation change that occurs the other three will bind much more easier than the first.

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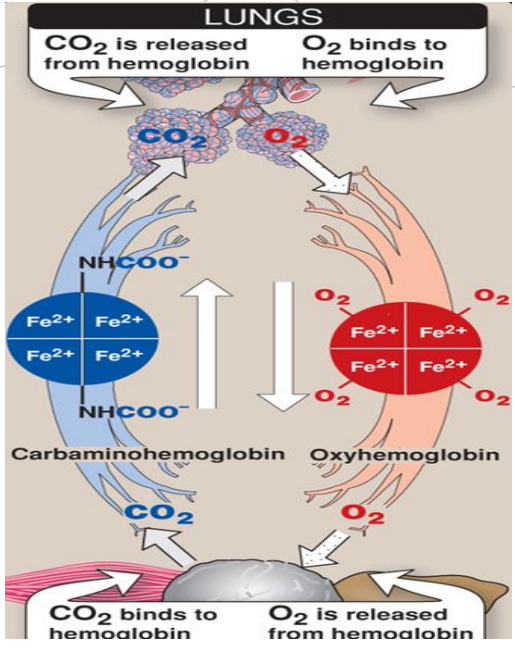
Hemoglobin function

Normal value of hemoglobin (g/dL):
- Males 14-16
- Females 13-15

Carries CO_2 (carbon dioxide) and protons from tissue back to lungs

- Low PO_2 causes hemoglobin to release O_2
- High PCO_2 allows O_2 to bind to hemoglobin
- HB that is bound to CO2 is called carbaminohemoglobin



Carries O_2 from lungs to tissue

- High PO_2 causes hemoglobin to bind to O_2 and be 100% saturated (all 4 hemoglobin binding places are occupied)
- HB that is bound to oxygen is called oxyhemoglobin

* a:alfa

Types of normal Hemoglobin

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Hb A2

- Appears shortly before birth.
- Constitutes ~2% of total Hb.
- Composed of two (a) and two (δ **delta)** globin chain*.
- It produced by the 8th month of pregnancy in the fetus and it replaces Hb F gradually. (بالحالات المرضية يصير في طفرة بالبيتا تؤدي الى تكاثر هالنوعين)

Hb F

- Major hemoglobin found in the fetus and newborn
- Tetramer (has 4 monomers) with two alpha and two **gamma** (γ) chains
- Higher affinity for O2 than Hb A Why? Because there is a molecule that binds to beta subunit which release O2 easily, and found less with gamma subunit.
- It allows the fetus to take the O2 from the mother's blood.
- Transfers O2 from maternal to fetal circulation across placenta.
- It's produced from the 5th week until 6 months after born.

Hb A 1C

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA1c levels are high in patients with diabetes mellitus.
- When glucose is high, it will bind to the hemoglobin.
- It's a diagnostic tool of diabetes since it gives a reflect image about the last 2-3 months

- 5.8% is the normal range.
- 6.4% is high risk range.
- >= 6.5% indicates diabetes.

Abnormal hemoglobin

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Unable to transport O_2 due to abnormal structure

Carboxy-Hb:	**Met- Hb**:	**Sulf-HB**
• CO "carbon monoxide" replaces O_2 and binds 200X tighter than O2 • Found in in smokers, and causes shortness of breath • Also found in carbon monoxide poisoning • It is treatable by high amounts of 100% saturated oxygen	• Contains oxidized Fe^{3+} **(ferric)** (~2%) that cannot carry O_2 (normal HB binds to ferrous "reduced form of iron) • reversible reaction • This kind of hemoglobin is normally produced in the body. But we convert it to normal hemoglobin by the enzyme Nadh • Nadh reduces ferric iron to ferrous. A deficiency (genetic) in this enzyme causes this kind of abnormal hemoglobin • Drugs like nitrate, acute inflammation, and production of oxygen reactive species are other causes of this abnormality	• Forms due to high sulfur levels in blood • (irreversible reaction) • Seen in people treated with sulfate or cases of chronic constipation

Hemoglobinopathies

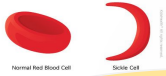
Disorders of hemoglobin caused by:

-Synthesis of structurally abnormal Hb (qualitative) Or -Synthesis of insufficient quantities of normal Hb (quantitative)

Or

-A combination of both

-Beta subunit is represented by one gene
-Alpha is represented by two genes "genetic defects are less common because there are two gene responsible for the same functions



Sickle cell (HbS) disease

-Caused by a single mutation in b-globin gene (point mutation)
-Glutamic acid at position 6 in HbA is replaced by valine
-The mutant HbS (abnormal, modified HB) contains βs chain
2copys
-The shape of RBCs become sickled, with a lifespan of 20 days
-Causes sickle cell anemia

Glutamic acid is has a polar group while valine is non polar, this leads to structural changes where the modified hemoglobin starts attaching to itself making polymers of hemoglobin giving it its sickled shape

Hemoglobin C disease

-Caused by a single mutation in b-globin gene
-Glutamic acid at position 6 in HbA is replaced by **lysine** (polar +) (notice it is the same position as sickle cell anemia but instead of valine it becomes lysine)
-Causes a mild form of hemolytic anemia

Methemoglobinemia

-Caused by oxidation of Hb to ferric (Fe3+) state
-Methemoglobin cannot bind oxygen
-Caused by certain drugs, reactive oxygen species and NADH-cytochrome b5 reductase deficiency
-can be treated except in case of enzyme deficiency
-Chocolate cyanosis: brownish-blue color of the skin and blood

Thalassemia

-Defective synthesis of either α or b-globin chain due to gene mutation. Has two types:
(1) α-thalassemia:
-Synthesis of α-globin chain is decreased or absent
-Causes mild to moderate hemolytic anemia
(2) b-thalassemia:(احتمالية الإصابة اسهل)
-Synthesis of b-globin chain is decreased or absent
-Causes severe anemia
-Patients need regular blood transfusions
-can be minor which doesn't require blood transfusions , or major which requires blood transfusions

Summary

Summary of Hemoglobinopathies

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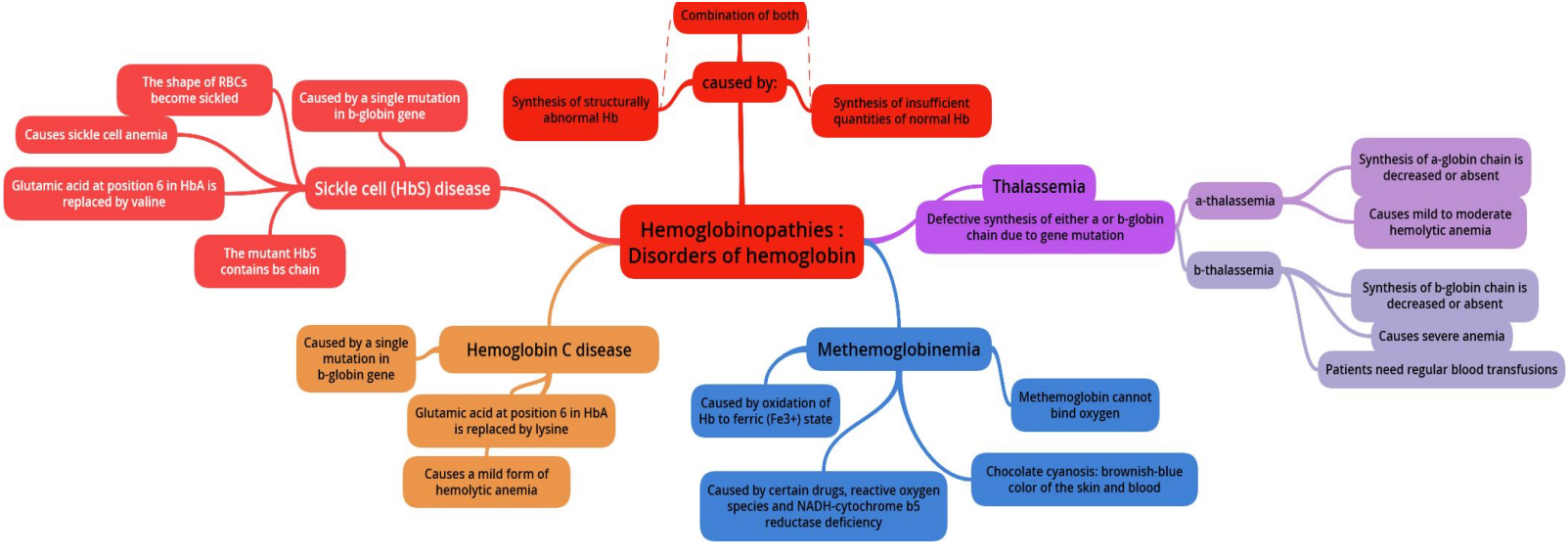

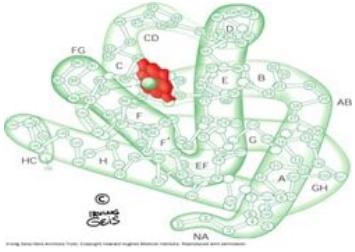

Myoglobin

Looks like one subunit of HB but with some differences

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A globular heme protein in heart and "skeletal" muscle

Function:

- ★ Stores and supplies oxygen to the heart and skeletal muscle only.
- ★ It gives red color to skeletal muscles.
- ★ Supplies oxygen during aerobic exercise.

structure :

- ★ Contains a single polypeptide chain forming a single subunit with eight a-helix structures
- ★ The interior of the subunit is composed of nonpolar amino acids
- ★ The charged (polar) amino acids are located on the surface (forming hydrogen bond) while The heme group is present at the center of the molecule
- ★ Has one heme group which means it binds to one O2

Myoglobin in diseases:

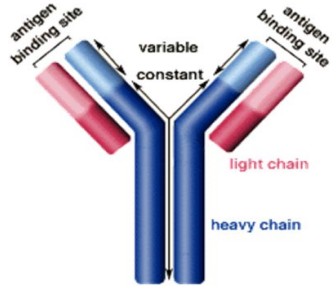
- ★ **Myoglobinuria:** Myoglobin is excreted in urine due to muscle damage (rhabdomyolysis) it means the destruction of muscle cells
- ★ May cause acute renal failure (block of urine)
- ★ Specific marker for muscle injury
- ★ Less specific marker for heart attack

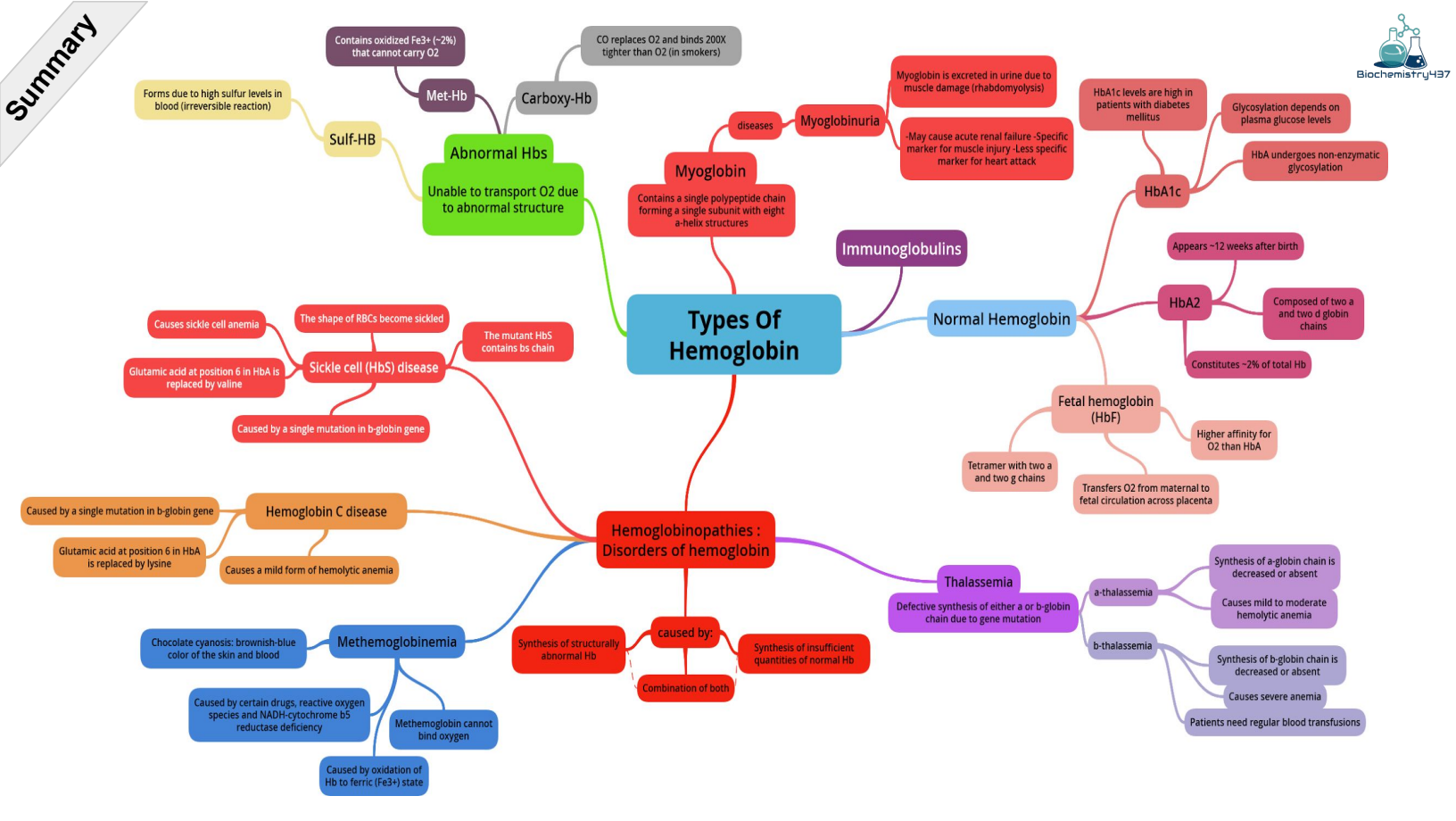
Differences between a subunit of HB and myoglobin

Subunit of HB	Myoglobin
hydrophilic groups on the surface	hydrophilic groups on the surface
Some hydrophobic groups are on the surface for intra-dimer binding	All hydrophobic groups are inside
One histidine group involved in binding	Two histidine groups. - one involved in binding - The other facilitates the binding

Immunoglobulins

- Defensive proteins produced by the B-cells of the immune system
- **Y-shaped** structure with 2 heavy and 2 light polypeptide chains
- The top part of the heavy and the light chains make the antigien binding site, which is variale
- The lower part of the heavy chain makes the constant region -for all Ig-
- Neutralize bacteria and viruses (meaning they bind to the bacteria to make it detectable by the macrophages)
- Types: IgA, IgD, IgE, IgG, IgM




Summary
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Types Of Hemoglobin
Normal Hemoglobin
Immunoglobulins
HbA1c
HbA1c levels are high in patients with diabetes mellitus
Glycosylation depends on plasma glucose levels
HbA undergoes non-enzymatic glycosylation
HbA2
Appears ~12 weeks after birth
Composed of two a and two d globin chains
Constitutes ~2% of total Hb
Fetal hemoglobin (HbF)
Higher affinity for O2 than HbA
Tetramer with two a and two g chains
Transfers O2 from maternal to fetal circulation across placenta
Myoglobin
Contains a single polypeptide chain forming a single subunit with eight a-helix structures
diseases
Myoglobinuria
Myoglobin is excreted in urine due to muscle damage (rhabdomyolysis)
-May cause acute renal failure -Specific marker for muscle injury -Less specific marker for heart attack
Abnormal Hbs
Unable to transport O2 due to abnormal structure
Met-Hb
Contains oxidized Fe3+ (~2%) that cannot carry O2
Carboxy-Hb
CO replaces O2 and binds 200X tighter than O2 (in smokers)
Sulf-HB
Forms due to high sulfur levels in blood (irreversible reaction)
Hemoglobinopathies : Disorders of hemoglobin
Sickle cell (HbS) disease
Causes sickle cell anemia
The shape of RBCs become sickled
The mutant HbS contains bs chain
Glutamic acid at position 6 in HbA is replaced by valine
Caused by a single mutation in b-globin gene
Hemoglobin C disease
Caused by a single mutation in b-globin gene
Glutamic acid at position 6 in HbA is replaced by lysine
Causes a mild form of hemolytic anemia
Methemoglobinemia
Chocolate cyanosis: brownish-blue color of the skin and blood
Caused by certain drugs, reactive oxygen species and NADH-cytochrome b5 reductase deficiency
Methemoglobin cannot bind oxygen
Caused by oxidation of Hb to ferric (Fe3+) state
caused by:
Synthesis of structurally abnormal Hb
Synthesis of insufficient quantities of normal Hb
Combination of both
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Defective synthesis of either a or b-globin chain due to gene mutation
a-thalassemia
Synthesis of a-globin chain is decreased or absent
Causes mild to moderate hemolytic anemia
b-thalassemia
Synthesis of b-globin chain is decreased or absent
Causes severe anemia
Patients need regular blood transfusions

Take home messages

1-Amino acid chains fold into shapes that resemble spheres are called globular proteins.

2- Fibrous proteins are mainly insoluble, while globular proteins are soluble structural proteins.

3- Hb, Myoglobin, globulines and enzymes are examples of globular proteins.

4-Functionally, Hb is for O2 and CO2 transport.

5-HbA, HbA2 and HbF are examples of normal Hb, in which the tetrameric structure is composed of 2α constant subunits with 2 changeable β subunits according to Hb type.

6- HbA1C is a HbA which undergoes non-enzymatic glycosylation, depending on plasma glucose levels.

7- Carboxy-Hb, Met-Hb and Sulf-Hb are examples of abnormal Hb, in which O2 molecules are not transported due to abnormal Hb structure.

8- Disorders of Hb caused by synthesis of structurally abnormal Hb and/or insufficient quantities of normal Hb.

9- Sickle cell (HbS) and HbC diseases are caused by a single mutation in β-globin gene.

10-Glu6 in HbS is replaced by Val, while it is replaced by Lys in HbC.

11-Methemoglobinemia is caused by oxidation of Hb, inhibiting O2 binding leading to chocolate cyanosis.

12- Thalassemia is caused by a defect in synthesis ofeither α- or β-globulin chain, as a result of gene mutation.

13- α-Thalassemia causes less sever anemia than β Thalassemia.

14- Myoglobin is a globular heme protein, which stores and supplies O2 to the heart and muscle onHb is composed of 4 chains (subunits), while Myoglobin is composed of a single chain.

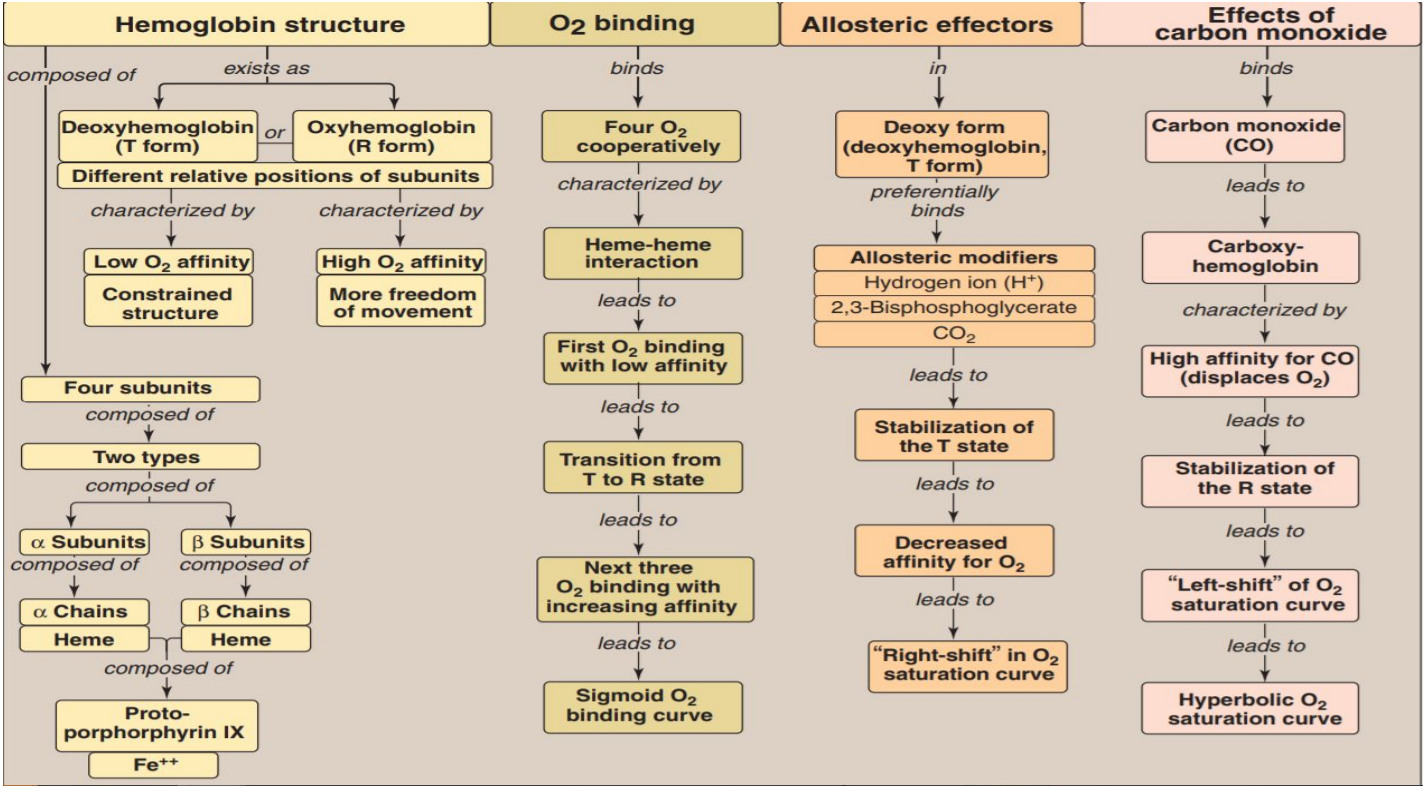
15-Myoglobinuria is a specific marker for muscle injury and may cause acute renal failure.

16- Immunoglobulins are defensive proteins produced by the B-cells.

17- Immunoglobulins consist of 5 types: IgA, IgD, IgE, IgG and IgM.Iy.

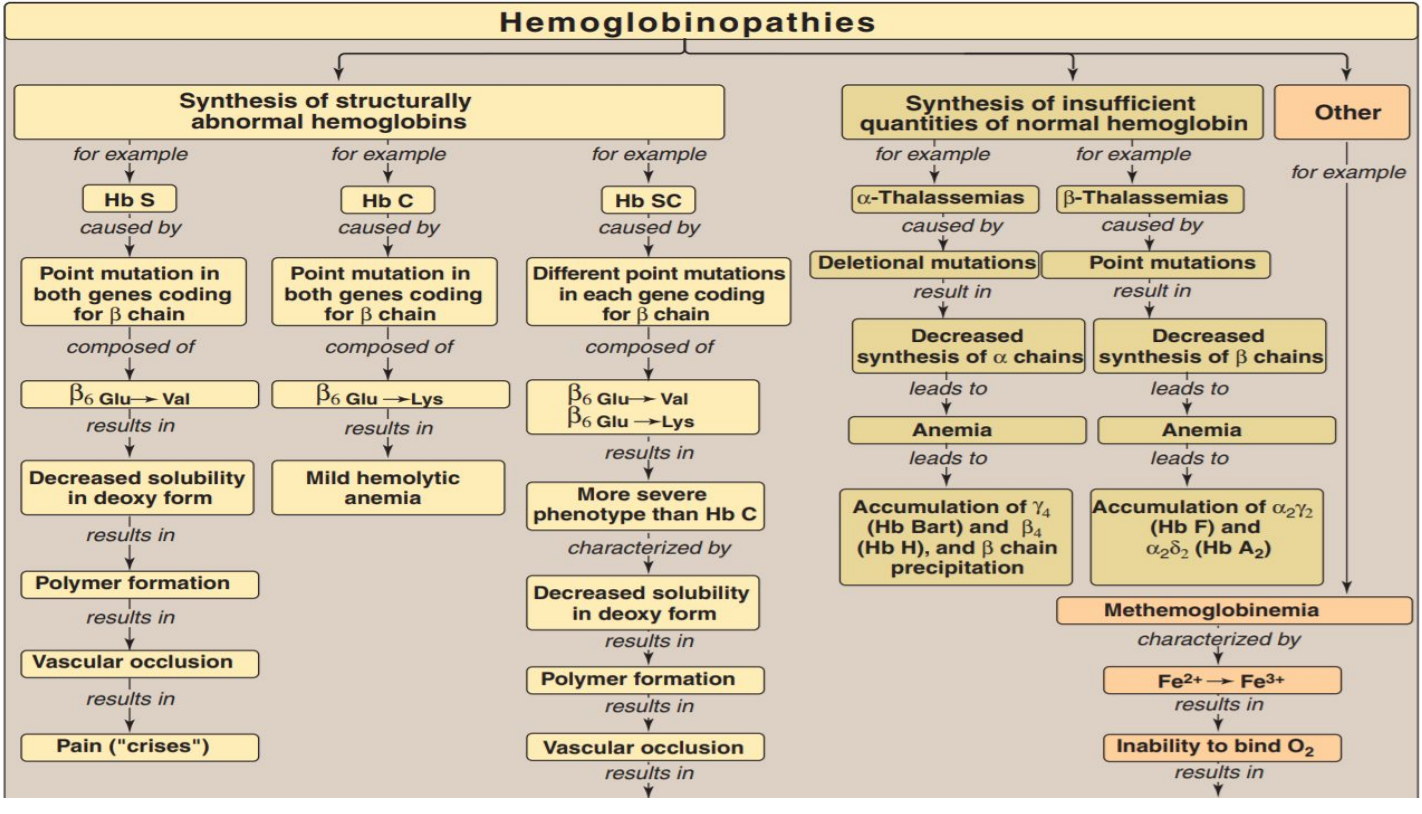
Extra

Key concept map for hemoglobin structure and function (from lippincott)



Extra

Key concept map for hemoglobinopathies (from lippincott)



Extra

Lippincott summary

Hemoglobin A, the major hemoglobin in adults, is composed of four polypeptide chains (two α chains and two β chains, α2β2) held together by noncovalent interactions (Figure 3.24). The subunits occupy different relative positions in deoxyhemoglobin compared with oxyhemoglobin. The deoxy form of hemoglobin is called the “T,” or taut (tense) form. It has a constrained structure that limits the movement of the polypeptide chains. The T form is the low-oxygen-affinity form of hemoglobin. The binding of oxygen to hemoglobin causes rupture of some of the ionic and hydrogen bonds. This leads to a structure called the “R,” or relaxed form, in which the polypeptide chains have more freedom of movement. The R form is the high-oxygen-affinity form of hemoglobin. The oxygen dissociation curve for hemo globin is sigmoidal in shape (in contrast to that of myoglobin, which is hyperbolic), indicating that the subunits cooperate in binding oxygen. Cooperative binding of oxygen by the four subunits of hemoglobin means that the binding of an oxygen molecule at one heme group increases the oxygen affinity of the remaining heme groups in the same hemoglobin molecule. Hemoglobin’s ability to bindoxygen reversibly is affected by the pO2 (through heme-heme interactions), the pH of the environment, the pCO2, and the availability of 2,3-bisphosphoglycerate (2,3-BPG). For example, the release of O2 from Hb is enhanced when the pH is lowered or the pCO2 is increased (the Bohr effect), such as in exercising muscle, and the oxygen dissociation curve of Hb is shifted to the right. To cope long-term with the effects of chronic hypoxia or anemia, the concentration of 2,3-BPG in RBCs increases. 2,3-BPG binds to the Hb and decreases its oxygen affinity, and it, therefore, also shifts the oxygen-dissociation curve to the right. Carbon monoxide (CO) binds tightly (but reversibly) to the hemoglobin iron, forming carbon monoxy hemoglobin (Hb CO). Hemoglobinopathies are disorders caused either by production of a structurally abnormal hemoglobin molecule, synthesis of insufficient quantities of normal hemoglobin subunits, or, rarely, both (Figure 3.25). The sickling diseases sickle cell anemia (Hb S disease) and hemoglobin SC disease, as well as hemoglobin C disease and the thalassemia syndromes are representative hemoglobinopathies that can have severe clinical consequences.

MCQs:

1- What is the function of Myoglobin ?
A- oxygen transport B- oxygen storage C- exchange gas D-none

2- A Hb molecule contains …….. Carries …….
A- 4 heme groups , 2 molecules of O2
B- 2 heme groups , 2 molecules of O2
C- 4 molecules of O2 , 4 heme groups
D-4 heme groups , 4 molecules of O2

3- Which of the following has highest affinity to O2 ?
A- HbA B-HbA2 C-HbF D-HbA1c

4- Caused by Glutamic acid at position 6 in HbA is replaced by lysine
A-Thalassemia B- sickle cell anemia C-Methemoglobinemia
D-Hemoglobin C disease

Answers
1-B
2-D
3-C
4-D

SAQ

A 67-year-old man presented to the emergency department with a 1 week history of angina and shortness of breath. He complained that his face and extremities had a “blue color.” His medical history included chronic stable angina treated with isosorbide dinitrate and nitroglycerin. Blood obtained for analysis was chocolate-colored.

What is the most likely diagnosis?

What is the cause of the disease ?

Correct answer = . Methemoglobinemia; Oxidation of the heme component of hemoglobin to the ferric (Fe3+) state forms methemoglobin. This may be caused by the action of certain drugs, such as nitrates. The methemoglobinemias are characterized by chocolate cyanosis (a brownish-blue coloration of the skin and mucous membranes), and chocolate-colored blood as a result of the dark-colored methemoglobin. Symptoms are related to tissue hypoxia, and include anxiety, headache, dyspnea. In rare cases, coma and death can occur.

Team leaders

- محمد حسن حكيم
- رهام الحلبي

Boys team

- طارق العميم
- عبدالرحمن التركي
- داوود اسماعيل
- صالح الوكيل
- سعيد آل سرار
- عبدالملك الشرهان
- عدنان المقبل
- محمد ابراهيم
- عبدالله الحربي

Girls team

- الهنوف الجلعود
- رهف الشنيبر
- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
- ريناد الغريبي
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